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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/164,568	10/01/98	NOELLE R	012712-572

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EXAMINER	
GAMBEL, P	
ART UNIT	**PAPER NUMBER**
1644	9

DATE MAILED: 10/04/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/164,568	NOELLE ET AL.
Examiner	**Group Art Unit**
GAMBEL	1644

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication .
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

☑ Responsive to communication(s) filed on 7/10/00.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 1 1; 453 O.G. 213.

Disposition of Claims

☑ Claim(s) 54-63 is/are pending in the application.

Of the above claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☑ Claim(s) 54-63 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The specification is objected to by the Examiner. APPLICATION SHOULD UPDATE THE STATUS OF PRIORITY DOCUMENTS.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119 (a)-(d)

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 11 9(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 1 7.2(a)).

*Certified copies not received: _____.

Attachment(s)

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☑ Notice of Reference(s) Cited, PTO-892

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Interview Summary, PTO-413

☐ Notice of Informal Patent Application, PTO-152

☐ Other _____

Office Action Summary

DETAILED ACTION

1. Applicant's election without traverse of Group II in Paper No. 8 is acknowledged.

Upon reconsideration, including applicant's arguments; gp39-specific and soluble CD40 as gp39 antagonists will be examined in the instant application.

Claims 54-63, as they read on "autoantigen expressing cells" are being acted upon as the elected invention.

Claims 1-53 have been canceled previously.

2. For examination purposes, it is noted that gp39 is the same as the CD40 ligand / CD40L /CD154.

3. No Information Disclosure Statement has been filed with the instant application.

4. Formal drawings have been submitted which comply with 37 CFR 1.84.

5. The application is required to be reviewed and all spelling, TRADEMARKS, and like errors corrected.

Trademarks should be capitalized or accompanied by the ™ or ® symbol wherever they appear and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the trademarks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Appropriate corrections are required

6. The following is a quotation of the first paragraph of 35 U.S.C. § 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 54-63 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention

Upon review of the art on treating established immune responses, particularly those of antigen primed immune systems such as autoimmune diseases, encompassed by the claimed methods; the following is noted.

In vitro and animal model studies have not correlated well with in vivo clinical trial results in patients. Since the therapeutic indices of immunosuppressive drugs such as costimulatory-based biopharmaceutical drugs can be species- and model-dependent, it is not clear that reliance on the experimental observations of inhibiting certain in vitro or in vivo immune response would be predictive of treating the breadth of autoimmune diseases encompassed by the claimed methods. There is insufficient objective evidence that accurately reflects the relative efficacy of the claimed therapeutic strategies to inhibit autoimmune diseases, commensurate in scope with the therapeutic methods encompassed by the claimed methods.

Pharmaceutical therapies in the absence of in vivo clinical data are unpredictable for the following reasons; (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

Bach (TIPS, 14: 213-216, 1993) reiterates these aspects of immunosuppressive therapy of autoimmune diseases with antibodies directed against T cells (see entire document). Although there has been some success with CD4 in psoriasis and perhaps arthritis, Bach clearly indicates that autoimmune disease cannot be considered as a whole and treatment selection must be considered with each disease (page 213, column 3). Also T cell intervention does not have the same sensitivity in each disease. Bach also reviews the art-known resistance of autoimmunity to therapeutic intervention (page 215, column 3).

The claimed methods encompass treating any number of autoimmune diseases. In contrast to acute conditions, the chronic and complicated nature of the targeted disorders encompassed by the claimed methods are diagnosed only after significant tissue damage has occurred and have an ongoing immune response. With respect to treating various inflammatory conditions with CD40-CD40 ligand antagonists in the face of an ongoing or established immune response, the following limitations have been noted.

Stuber et al. (J. Exp. Med. 183: 693-698, 1996) disclose when ant-gp39 was given after the disease was established, no effect on the disease activity was observed (see entire document, including Abstract and Discussion). Here, Stuber et al. distinguishes between treating acute conditions such as transplant rejection versus chronic conditions such as autoimmune diseases (see Discussion, last paragraph).

Gray et al. (J. Exp. Med. 180: 141-155, 1994) teaches that the secondary response was not readily blocked by sCD40-γ1 treatment, indicating a relative independence of CD40 ligation of antigen-experienced B cells (see entire document, including Abstract). Here, if sCD40-γ1 were delayed until day 4 of the primary response, mice develop normal and possibly enhance memory responses.

Resetkova et al. (Thyroid 6: 267- 273, 1996) discloses observations on a model to determine the role of interactions between gp39 and CD40 in an established human Graves' disease and showed immunosuppressive effects on humoral response by directly blocking CD40-gp39 interactions in vivo (see entire document). However, this reference also clearly recognizes the limitations of such experimental observations by stating that it is not clear how anti-gp39 would function in an individual with Graves' disease with an intact immune system (page 272, column 2, paragraph 1). Moreover, inhibition of humoral responses achieved by anti-gp39 in this study was only partial and it is not clear if this would lead to complete remission. The dosage necessary to achieve the optimal results shown in this study may be proportionally too high to be practical in the treatment of human autoimmune thyroid disease and might lead to immune compromise.

Biacone et al. (Kidney Int. 48: 458-468 1995) teach that soluble CD40 fusion protein can inhibit antibody-mediated glomerular disease if provided in a narrow window of early immune response but that this antagonist was not effective in reversing established disease (see entire document, including the Discussion, particularly the last two paragraphs).

The following is consistent with the lack of predictability of treating autoimmune diseases with CD40:CD40L antagonists such as anti-CD40L antibodies, which is the active ingredient of the claimed methods.

Two Biogen Press Releases (10/21/99; 11/2/99) have indicated the halting of ongoing clinical trials, including its application to Factor VIII inhibitor syndrome, transplantation, multiple sclerosis, ITP and lupus nephritis, with Antova, which is the humanized CD40L-specific antibody.

Similarly, Seachrist (BioWorld Today 10 (204) : 1,3, 10/25/99) discloses the halting of clinical trials using the humanized CD40-ligand specific antibody Antova. It is noted that this article discloses that a biotech analyst believes that the anti-CD40L antibody Antova is dead in its present form.

Further a Press Release from IDEC Pharmaceuticals, Inc. (4/20/00) indicates that treating SLE with another anti-CD40L antibody was not significantly different from that observed in the control group where a marked placed effect was noted and, in turn, the Phase III Development program will not be pursued at this time.

Therefore, the reliance upon observations wherein the CD40-CD40 ligand antagonists are administered at the same time as initial stimulus or insult may inhibit certain immune responses, including humoral and cellular immunity. Even though subsequent secondary responses may be affected, such observations still rely upon inhibiting activation of T cells at the onset or initiation of experiencing the antigen or stimulus and not upon experiencing an ongoing responses wherein secondary responses or antigen experienced lymphocytes are already in place. In contrast the claimed methods encompass using anti-CD40L antibodies to treat autoimmune diseases wherein the diagnosis of such diseases occur after antigen priming has occurred.

CD40-CD40 ligand antagonists appear to inhibit the onset or activation of the immune response. In contrast, CD40-CD40 ligand antagonists do not appear to inhibit an established or ongoing immune or inflammatory responses, encompassed by the claimed methods, as evidenced by the references of record and set forth herein.

In reviewing antigen-specific immunotherapy, Tisch et al. (PNAS 91: 437-438, 1994) disclose that it is apparent that peptide- or antigen-specific T immunotherapy, when applied to a highly defined model of autoimmunity, can be effective. However it is unclear whether this approach is feasible in the prevention or treatment of spontaneous autoimmune disease such as multiple sclerosis, diabetes or arthritis, in which the target autoantigens are not known and a number of autoantigens appear to be involved in the disease process). Furthermore, it is unclear whether such immunotherapy can be used to treat an ongoing autoimmune response (which is the usual case) or whether it is effective only in terms of prevention. Generally, such diseases are diagnosed only after significant tissue damage has occurred. Human autoimmune diseases comprise multiple epitopes or multiple immune responses that makes therapeutic intervention a major hurdle even for known autoimmune conditions.

Therefore, it is not clear that the skilled artisan could predict the efficacy of the CD40L-specific antibodies to inhibit autoimmune diseases, commensurate in scope with the claimed methods.

In view of the lack of predictability of the art to which the invention pertains the lack of established clinical protocols for effective antibody-based therapies on inhibiting human autoimmunity; undue experimentation would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed methods and absent a sufficient number of working examples providing evidence which is reasonably predictive that the claimed methods are effective for inhibiting human autoimmunity with CD40L-specific antibodies.

8. Claims 54-63 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The specification broadly describes and the claims recite as part of the invention the following:

"An autoantigen expressing cell(s)".

The instant methods which rely upon "autoantigen expressing cells" rely upon possession or knowledge of the "autoantigen" in order to express in an antigen presenting cell.

Such autoantigens do not meet the written description provision of 35 USC 112, first paragraph. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.).

The skilled artisan cannot envision all the contemplated "autoantigens" encompassed by the by the detailed chemical structure of the claimed autoantigens and therefore conception cannot be not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself (or in this case the autoantigen) is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481, 1483. In Fiddes v. Baird, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class.

Similarly, applicants have not disclosed sufficient information encompassing "autoantigens" and therefore clearly lacks written description for the broad class of "autoantigen expressing antigen presenting cells".

As pointed out above and in reviewing antigen-specific immunotherapy; Tisch et al. (PNAS 91: 437-438, 1994) disclose that it is apparent that peptide- or antigen-specific T immunotherapy, when applied to a highly defined model of autoimmunity, can be effective. However, it is unclear whether this approach is feasible in the prevention or treatment of spontaneous autoimmune disease such as multiple sclerosis, diabetes or arthritis, in which the target autoantigens are not known and a number of autoantigens appear to be involved in the disease process.

Therefore, it does not appear that the limited disclosure of known antigens in experimental systems in the specification as filed provides written description of the "autoantigens", particularly those involved human autoimmunity, where the autoantigens are either unknown or encompass a myriad of autoantigens, which can change during the course of the disease.

While the specification as filed discloses certain known antigens; the specification does not provide sufficient disclosure of "autoantigens", which would be presented by antigen presenting cells that meets the written description provision of 35 USC 112, first paragraph.

Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.).

Applicants are directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 64, No. 244, pages 71427-71440, Tuesday December 21, 1999.

9. Claim 57 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 57 is indefinite in the recitation of "professional" antigen presenting cell. While it is acknowledged that page 9, paragraph 3 of the instant specification discloses that "professional" antigen presenting cells may be "monocytes, dendritic cells or Langerhans's cells; the metes and bounds of such "professional" APC's are unclear and ambiguous. It is unclear what differs a professional APC from an APC, provided that a cell presents antigen.

Applicant is invited to recite the particular cell types, disclosed in the specification as filed.

Applicant should specifically point out the support for any amendments made to the disclosure. See MPEP 714.02 and 2163.06

10. No claim allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November

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September 25, 2000